stryker BIOTECH

OP-1 IMPLANT PACKAGE INSERT

HUMANITARIAN DEVICE. OP-1 Implant is authorized by Federal law for use as an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative treatments have failed. The effectiveness of this device for this use has not been demonstrated.

Caution: Federal law restricts this device to sale by or on the order of a physician.

PRODUCT DESCRIPTION:
OP-1 Implant is an osteoinductive and osteoconductive bone graft material. It is supplied in a glass vial containing one gram of the device in the form of a sterile dry powder comprised of recombinant human Osteogenic Protein 1 (OP-1 or BMP-7) and bovine bone collagen.

Self-adhesive patient labels indicating the lot number of the implant are provided for the user's convenience.

STORAGE CONDITIONS:
Store OP-1 Implant at 2-8 °C.

INDICATIONS:
OP-1 Implant is indicated for use as an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative treatments have failed.

CONTRAINDICATIONS:
- OP-1 Implant should not be used to treat patients who have a known hypersensitivity to the active substance or to collagen.
- OP-1 Implant should not be applied at the site of a resected tumor which is at or near the vicinity of the defect/fracture or in patients with a history of malignancy.
- OP-1 Implant should not be administered to patients who are skeletally immature (<18 years of age or no radiographic evidence of closure of epiphyses).
- OP-1 Implant should not be administered to pregnant women. The potential effects of OP-1 treatment on the human fetus have not been evaluated. Studies in rats injected with high doses of OP-1 have shown that small amounts of OP-1 will cross the placental barrier.

WARNINGS:
- Women of childbearing potential should be advised that antibody formation to OP-1 and its influence on fetal development have not been assessed. 38% of patients treated with OP-1 Implant and 13% of patients treated with autograft develop antibodies. The effect of maternal antibodies to OP-1 on the unborn fetus is unknown, both when the antibodies are detected during the first year following treatment and later, when the antibodies may not be detectable. Studies in genetically altered mice indicate that OP-1 is critical for fetal development and that lack of OP-1 activity, as might be induced by antibody, may cause neonatal death or birth defects.
- Women of childbearing potential should be advised to use contraception for one year following treatment with OP-1 Implant.
- The maximum human dose should not exceed 2 vials. In clinical studies treating nonunions requiring more than 2 vials, there was a higher incidence of failure.
- OP-1 Implant has no biomechanical strength to support fixation without a shared loading/stabilization adjunct (i.e., cast, instrumentation, etc.) in long bones. The following fixation methods have been utilized in clinical trials studying OP-1 Implant: cast/brace, external fixation, intramedullary rod and internal plate.
- Localized ectopic or heterotopic bone formation may occur outside of the treatment site.

PRECAUTIONS:
- Clinical studies using OP-1 Implant were performed in patients with nonunions resulting from trauma. There are no data regarding the use of OP-1 Implant in patients with nonunions resulting from bone diseases.
- OP-1 Implant may cause an immune reaction in some patients. The safety or probable benefit of OP-1 Implant in patients with autoimmune disease has not been demonstrated.
- The effect of radiation therapy, chemotherapy, immunosuppressive or steroid therapy on the probable benefit of OP-1 Implant is not known.
- There are no data on the excretion of OP-1 in the breast milk of patients who are nursing.
- OP-1 is important in the development of the kidney. Studies have not been performed to examine the neutralizing capacity of antibodies to OP-1 or their effect in patients with impaired renal function.
- IMMUNOGENICITY: As with all therapeutic proteins, there is a potential for immune responses to be generated against components of the OP-1 Implant. In the Tibial Nonunion clinical study, antibodies were detected to OP-1 (BMP-7) by an ELISA assay in 23/61 (38%) OP-1 treated patients and 8/61 (13%) autograft treated patients and confirmed by Western Blot analysis. The neutralizing capacity of these antibodies was not assessed. The significance of these antibodies is not known. The incidence of antibody detection is highly dependent on the sensitivity and specificity of the assay. The sensitivity of the antibody assay has not been adequately assessed and the actual incidence of antibodies could be higher. Additionally, the incidence of antibody detection may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to OP-1 Implant with the incidence of antibodies to other products may be misleading.
- A two year rat bioassay, in which approximately 17.5-70 times the equivalent maximum human dose of 2 vials of OP-1 Implant was placed under the skin, produced more cancer growths at the site of implantation of the OP-1 Implant compared to rats that had no OP-1 Implant. It is believed that this may be due to the Oppenheimer Solid State Tumor Effect, the formation of tumors at the site of implantation of inert objects under the skin in rats. This effect has not been reported in humans. Additional studies are ongoing to examine the effect of OP-1 on the growth of pre-existing tumors.
- Take care to ensure that OP-1 Implant will be contained by viable hard and soft tissue structures. Obtain adequate hemostasis before implanting OP-1 Implant to prevent the product from being displaced.
- Inadequate vascularity in the surrounding tissues may diminish the probable benefit of OP-1 Implant. Make every effort to surround the product with viable tissue.
- For single use only. Do not re-use OP-1 Implant. Discard unused product and use a new device for subsequent applications.
- Prior to use, inspect the packaging, vial and stopper for visible damage. If damage is visible, don't use the product. Retain the packaging and vial, and contact a Stryker Biotech representative.
- Do not use after the printed expiration date on the label.

ADVERSE EVENTS:
The following table is from two multicenter studies of OP-1 Implant in patients with long bone nonunions. Reported in the table are adverse events relevant to an orthopaedic procedure occurring in >1% of the total treated patients. Other less frequent and related events are listed in Table 1 below. No serious adverse events were attributed to the use of OP-1 Implant.

Table 1 - Summary of Adverse Events for All Patients in the Two Long Bone Nonunion Studies

Adverse Event Description	Tibial Nonunion Study OP-1 Implant n=61	Tibial Nonunion Study Autograft n=61	Long Bone Nonunion Study OP-1 Implant n=29
Musculoskeletal			
Hardware Complication	28/61	40/61	6/29
Nonunion	7/61	4/61	5/29
Osteomyelitis	6/61	15/61	7/29
Injury as a Result of Fall	3/61	3/61	2/29
Malunion	3/61	0/61	1/29
Hardware removal	2/61	1/61	0/29
Tendonitis (patellar, Achilles)	2/61	1/61	0/29
Contracture	1/61	3/61	1/29
Fracture (other)	1/61	3/61	0/29
Fracture (tibia, fibula)	1/61	3/61	1/29
Skin and Wound			
Wound Infection	18/61	14/61	5/29
Local Inflammation, rash, redness, itching	12/61	10/61	0/29
Swelling (ankle, foot, leg)	7/61	8/61	2/29
Blisters, skin abrasions	5/61	0/61	0/29
Neural			
Pain (ankle, knee, leg)	27/61	22/61	12/29
Neuralgia (numbness)	6/61	6/61	3/29
Pain (other)	3/61	3/61	3/29
Nerve Injury	2/61	2/61	0/29
Cardiovascular			
Hematoma	4/61	8/61	3/29
Anemia	4/61	5/61	1/29
Gastro-Intestinal			
Nausea, vomiting	18/61	19/61	3/29
Gastro-intestinal upset (indigestion, constipation, diarrhea)	7/61	5/61	1/29
Systemic and Other Complications			
Fever	31/61	29/61	0/29
Normal Surgical Complications	10/61	8/61	0/29
Drug Allergy (morphine, antibiotics)	2/61	5/61	1/29

Other events include: amputation of toe, aortocoronary bypass with valve replacement, arthritis, arthroscopy, arthrosis, athlete's foot, bruising, burning sensation, cardiac complications following surgery, chondrectomy, chondromalacia, cold symptoms/upper respiratory infection, death-unrelated causes, depression, dizziness, ear infection, fatigue, gangrene, headache/migraine, incontinence, insomnia, meniscal tear, muscle spasm, muscular herniation, myositis ossificans, nosebleeds, pancreatitis, peptic ulcer, plantar fascial fibromatosis, post operative bleeding, sciatica, skin graft, short term memory loss, shortness of breath, slow or decreased urination, stiffness, sweating, thrombophlebitis, thrombosis, urinary tract infection, weight loss, wound dehiscence, yeast infection.

Five (8%) OP-1 Implant patients reported 6 treatment related medical events, including persistent nonunion (3), erythema/swelling (2) and drainage (1).

Adverse event data has been collected from over 500 domestic and international patients treated with OP-1. Table 2 describes the incidence of cancer reported in these patients.

Table 2 – Incidence of Cancer in Patients Treated with OP-1 Worldwide

Cancer Type	Age	Sex	Time of Event Post-treatment with OP-1	Outcome
Pancreatic tumor with multiple metastases	83yrs.	Male	3 Months	Death
Gastric carcinoma	79yrs.	Male	9 Months	Recovered
Mantle cell lymphoma	76yrs.	Female	29 Months	Death
Right occipital basal cell carcinoma (non-healing forehead lesion)	60yrs.	Male	11 Months	Recovered
Recurrence of Chondrosarcoma	43yrs.	Female	6 weeks*	Death

* Treating physician believes recurrence may have presented on thalium scan prior to treatment with OP-1.

Five patients reported the occurrence of cancer. Four of the 5 events reported were non-osseous cancers occurring in elderly patients. A fifth event of recurring chondrosarcoma was reported in a patient with a history of chondrosarcoma. Recurrence and disease progression were considered normal for this type of cancer. The incidence of cancer in patients treated with OP-1 is less than 1% and is within the range of cancer occurrence in the general populations of the U.S. and Australia (the countries in which most patients were treated).

Eight (1.6%) out of more than 500 patients treated with OP-1 experienced 10 events related to urinary or renal systems. All 10 events were considered by the treating physicians as unrelated to study treatment and were mild to moderate in severity. No severe adverse events of this nature were reported. Events included urinary tract infection (5), slow urination (1), decreased urine output (1), urinary retention (1) and retrograde ejaculation (2). Many of these events were reported immediately post-treatment and can be attributed to catheterization during and after surgery.

PREPARATION FOR USE:

OP-1 Implant is intended to be reconstituted with sterile Sodium Chloride (NaCl) Injection, 0.9%, USP solution (saline).

1. Using sterile technique, remove the vial from its packaging.
2. Lift the plastic flip-top and remove the crimp from the vial.

Warning: Handle the crimp with care. The edges of the crimp are sharp and may cut or damage gloves.

3. Aligning your thumb with the internal gap of the stopper, pry up the edge of the stopper. Once the vacuum is broken, remove the vial stopper while holding the vial upright to prevent loss of product.

Warning: Do not insert a needle through the stopper. Puncture of the stopper with a needle may result in particles of stopper material contaminating the OP-1 Implant.

4. Utilizing a sterile syringe, carefully add 2-3 cc of sterile saline to OP-1 Implant in the vial. Begin with 2 cc and add saline to desired consistency. Use of more than 3 cc will result in a less cohesive product which will be difficult to handle.
5. Mix the saline with the product in the vial using a sterile spatula or curette.
6. The product will expand to a maximum volume (~4cc) within 2 minutes. Use the product promptly after reconstituting with saline.

RECOMMENDED TECHNIQUE:

1. Debride fibrous, necrotic or sclerotic tissue and, when appropriate, decorticate bone so that OP-1 Implant will directly contact viable osseous tissue.
2. Provide adequate hemostasis to ensure that the material stays at the surgical site. Irrigate the surgical site as necessary, prior to placement of OP-1 Implant. Where practical, surgical manipulations to the site should be completed prior to device implantation.
3. Remove the reconstituted OP-1 Implant from the vial with a sterile instrument such as a spatula or curette.
4. Apply OP-1 Implant to the prepared osseous tissue site. The amount of material used should approximate the size of the bone defect.

   Warning: Do not use suction or irrigation directly at the implant site as this may remove particles of OP-1 Implant. Remove excess fluid by suctioning adjacent to the implant site or carefully blotting the area with a sterile sponge.
5. Close soft tissues around the defect containing OP-1 Implant using suture material of choice. Closure is critical for containment and maintenance of OP-1 Implant particles in the area of the defect.
6. After closure of the soft tissue around the defect, irrigate field, if necessary, to remove any stray particles.

Do not place a drain directly in the implant site. Place it subcutaneously if possible.

CLINICAL EXPERIENCE:

Clinical experience with OP-1 Implant in the intended indication is summarized below. In a multicenter Tibial Nonunion Study, a subset of 14 patients with prior failed autograft were treated with OP-1 Implant. In a second multicenter Long Bone Treatment Study, 10 patients with long bone nonunions having prior failed autograft were treated with OP-1 Implant. Results are shown in Tables 3 and 4 below:

Table 3 - Tibial Nonunion Study Results– Prior autograft patients only

Analysis at 9 Months	OP-1 Implant N=14	Autograft N=13
Overall	7/14	11/13
Clinical (Pain and Function)	12/14	12/13
Radiographic (Bridging in 3 views)	8/14	12/13

Table 4 - Long Bone Treatment Study Results

Analysis at 9 Months	OP-1 Implant N=10
Overall	1/10
Clinical (Pain and Function)	7/10
Radiographic (Bridging in 3/4 cortices)	2/10

Manufactured by

stryker BIOTECH

Registration # 9045977
35 South Street
Hopkinton, MA 01748 USA
Phone (508) 416-5200
www.op1.com

A division of
Stryker Corporation
2725 Fairfield Road
Kalamazoo, MI 49003